**REMARKS**

Claims 21, 23 to 25 and 27 to 31 are currently pending in the subject application. Applicants have not cancelled, added or amended any claims herein. Applicants have hereinabove amended the first paragraph of the specification to correct the priority paragraph of the specification.

**Declaration**

The Examiner indicated that the Declaration is defective because not all of the applications listed in the priority paragraph of the specification are listed in the Declaration.

Applicants submit herewith as **Exhibit A** a Supplemental Application Data Sheet in compliance with 37 C.F.R. §1.76(c) to correct the benefit claimed. Specifically, the Supplemental Application Data Sheet enclosed herewith removes the claim to benefit of U.S. Serial Nos. 08/325,553, filed October 18, 1994, and 07/973,337, filed November 5, 1992. Applicants note that this removes the inconsistency between the benefit claimed in the priority paragraph of the specification and the benefit claimed in the inventors' declaration filed in connection with the above-identified application. Applicants further note that, pursuant to 37 C.F.R. §1.76(c)(1), a Supplemental Application Data Sheet may be provided to the United States Patent and Trademark Office at any time prior to payment of the issue fee. Accordingly, the attached Supplemental Application Data Sheet is being timely filed.

**Priority**

The Examiner stated that claims 21, 23-25 and 27-31 as amended on May 9, 2006 are drawn to a method of ablating, killing or eliminating a normal or prostate cancer cell comprising binding an antibody to an outer membrane domain of PSMA or binding an antibody bound to a substance effective to kill the cells. The Examiner asserted that PCT/US96/02424, of which benefit is claimed, does not provide adequate support for the method of ablating, killing or eliminating a normal or prostate cancer cell comprising binding an antibody to an outer membrane domain of PSMA. The Examiner asserted that claims 21, 23-25 and 27-31 would be treated by her as having a "current filing date" of January 2, 2004.

In response, applicants first note that the claims are in fact drawn to a method of ablating, killing, or eliminating normal, benign hyperplastic, and cancerous prostate epithelial cells comprising providing an antibody which binds to an outer membrane domain of prostate specific membrane antigen, as recited in claim 21, and a method according to claim 21 wherein the antibody is bound to a substance effective to kill, ablate or eliminate said cells upon binding of the antibody to the outer membrane domain of prostate specific membrane antigen of said cells, as recited in claim 27.

Applicants note that support for such a method can be found in the specification as originally filed (and in PCT/US96/02424), for example, at page 32, lines 23 to page 33, line 2, which discloses selecting hydrophilic amino acid sequences to generate antibodies. In addition, page 32, lines 14 to 17 of the specification as originally filed (and PCT/US96/02424) recite that "with the protein sequence information, antigenic areas may be identified and *antibodies directed against these areas may be generated and targeted to the prostate cancer* for imaging the cancer *or therapies.*" (Emphasis added). Accordingly, applicant maintains that support for the claimed method is found in the specification, and in PCT/US96/02424 of which benefit is claimed.

**Claims rejected under 35 U.S.C. §112 (Second Paragraph)**

The Examiner rejected claims 21, 23-25 and 27-31 under 35 U.S.C. §112, second paragraph, as allegedly indefinite as to "how the cells are killed, ablated or eliminated by an antibody". The Examiner asserted that it is not clear "how the antibody alone bind[s] to the surface of the cells and kills the cells."

In response, applicants respectfully traverse the Examiner's rejection. Applicants note that antibody-dependent cell-mediated cytotoxicity is one such art-recognized mechanism. In support of this position, applicants submit copies of two abstracts, Nabioullin et al. and Kinouchi et al., copies of which are attached hereto as **Exhibits B and C**, respectively. These abstracts discuss the role of antibody-dependent cell-mediated

cytotoxicity in cancer therapy. Accordingly, applicants maintain that one skilled in the art would understand that antibodies may mediate cell death.

The Examiner also stated that it is also not clear how antibody is bound to a substance effective to kill, ablate or eliminate cells as recited in claim 27. The Examiner further stated that it is not clear whether "the substance is conjugated or not".

Applicants respectfully traverse the Examiner's rejection. Applicants note that conjugation to an antibody is one means by which a substance effective to kill, ablate or eliminate prostate cells can be bound to the outer membrane domain of prostate specific membrane antigen on cells. Applicants also maintain that the term "bound" as recited in claim 27 is readily understood by one of ordinary skill in the art. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Claims rejected under 35 U.S.C. §112 (First Paragraph, Written Description)**

The Examiner rejected claims 21 and 23-25 as failing to comply with the written description requirement "as drawn to new matter." The Examiner asserted that although the instant specification provides and teaches "that antibodies against PSM coupled with a cytotoxic agent will be useful to eliminate prostate cancer cells (page 68, line[s] 16-24) [it] does not provide sufficient support for the instant claims reciting eliminating

prostate cancer cell[s] or epithelial cells by an antibody only" (Examiner's emphasis).

In response, applicants respectfully traverse the Examiner's rejection. As applicants have noted hereinabove, the specification provides support for such therapies employing antibodies only, e.g. see page 32, lines 14 to 17 of the specification as originally filed (and PCT/US96/02424) which recite that "with the protein sequence information, antigenic areas may be identified and antibodies directed against these areas may be generated and targeted to the prostate cancer for imaging the cancer or therapies". Accordingly, applicants maintain that the claims as pending are sufficiently described in the specification as filed, and as such raise no issue of new matter.

The Examiner rejected claims 21, 23-25 and 27-31 under 35 U.S.C. §112, written description, asserting that the specification on pages 244-245 teaches a computer-predicted membrane-spanning domain of PSMA and states that this data enables prediction of inner and outer membrane domains which aids in designing antibodies for use in targeting and imaging prostate cancer. The Examiner asserted that the specification does not disclose any such antibodies, nor any method using such an antibody, to kill or eliminate cells of the prostate due to binding of the antibody to an outer membrane domain of PSMA. The Examiner further stated that the application does no more than describe the desired function of the claimed antibodies.

In response, applicants respectfully traverse the Examiner's rejection. Applicants note that the claimed method is described in the specification, and that one of ordinary skill in the art would recognize the description provided at, inter alia, page 32, lines 23 to page 33, line 2, which discloses selecting hydrophilic amino acid sequences to generate antibodies, and also at page 32, lines 14 to 17, which recite that "with the protein sequence information, antigenic areas may be identified and antibodies directed against these areas may be generated and targeted to the prostate cancer for imaging the cancer or therapies." Moreover, applicants maintain the computer prediction of hydrophobic and hydrophilic sequences, and generation of antibodies, were well-established and well-known techniques in the art by the effective filing date of the present application. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Claims rejected under 35 U.S.C. §112 (First Paragraph, Enablement)**

The Examiner rejected claims 21, 23-25 and 30-31 as not enabled by the specification. The Examiner asserted, inter alia, that the specification does not provide enablement for "antibody alone binding to an outer membrane domain of [a] prostate cancer cell to ablate, kill or eliminate [the] prostate cancer cell."

In response, applicants respectfully traverse the Examiner's rejection. Initially, applicants note that the specification, for example, at page 32, lines 14 to 17,

recites that "with the protein sequence information, antigenic areas may be identified and *antibodies directed against these areas may be generated and targeted to the prostate cancer* for imaging the cancer *or therapies.*" (Emphasis added). Clearly, the specification does teach therapies using antibodies. Furthermore the specification teaches obtaining antibodies to an outer membrane domain of PSMA, for example, at page 32, lines 23 to page 33, line 2, which discloses selecting hydrophilic amino acid sequences to generate antibodies. In addition, applicants note, as stated above, that antibody-dependent cell-mediated cytotoxicity is an example of an art-recognized mechanism of how antibody binding can effectuate cell death. Moreover, applicants further note that the level of skill in the art is high. Applicants thus maintain that *one of ordinary skill in the art* would readily be able to make and use the claimed invention given the teachings in the specification. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Claims rejected under 35 U.S.C. §103(a)**

The Examiner rejected claims 21, 23-25 and 30-31 under 35 U.S.C. §103(a) over Murphy et al. (Prostate, 28:266-271, 1996) in view of Horoszewicz et al. (Anticancer Research, 7:927-935, 1987) and Horoszewicz et al. (U.S. Patent No. 5,162,504, issued 1992). The Examiner stated that Murphy et al. teach an antibody 3F5.4G6 which "reacts with the extracellular domain of PSMA." The Examiner also stated that Murphy et al. do not teach a method of ablating, killing or eliminating prostate cancer cells by an

antibody or an antibody conjugated to a toxin. The Examiner further stated that Horoszewicz et al., (U.S. Patent No. 5,162,504), disclose a method of treating prostate cancer with prostate antigen specific antibody conjugated with a toxin. The Examiner further stated that Horoszewicz et al. (Anticancer Research, 7:927-935, 1987) "disclose 9H10-A4H, which only recognizes the surface of prostate cancer cells, LNCap." The Examiner asserted that "because Murphy et al., have shown the antibodies specifically bind to the extracellular domain (outer membrane domain) of prostate specific membrane antigen and Horoszewicz et al., have taught the method of treating prostate cancer cells by antibody-toxin conjugate, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to kill or eliminate the cancer cells with the method."

In response, applicants respectfully traverse the Examiner's rejection. Applicants note that the primary reference relied upon by the Examiner, Murphy et al., was published in April of 1996, i.e. after the February 24, 1995 effective filing date of the subject application, as well as after the filing date of PCT/US96/02424 (February 23, 1996). As such, Murphy et al. is not prior art to the claims pending in the subject application.

**SUPPLEMENTARY INFORMATION DISCLOSURE STATEMENT**

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following documents which are listed on the attached Form PTO-1449 (**EXHIBIT D**). Items 1-7 listed below are U.S. Patents or U.S. Patent Application Publications. No copies of these items are enclosed herewith as permitted by 37 C.F.R. §1.98(a)(2)(ii). Copies of items 8-11 below are attached hereto as **EXHIBITS 1-4** respectively:

1. U.S. Patent No. 7,105,159, Israeli et al., issued September 12, 2006;
2. U.S Patent No. 7,070,782, Israeli et al., issued July 4, 2006;
3. U.S. Patent No. 7,037,647, Israeli et al., issued May 2, 2006;
4. U.S. Patent No. 6,953,668, Israeli et al. issued October 11, 2005;
5. U.S. Patent No. 4,569,794, Smith et al., issued February 11, 1986;
6. Thorpe et al., U.S. Patent No. 5,855,866, issued Jan. 5, 1999;
7. U.S. Patent Application Publication No. 2006-0177450 A1, published August 10, 2006;
8. U.S. Serial No. 11/480,319, filed June 30, 2006;
9. Serval et al., (1990) J. Neurochem. 55: 39-46;
10. Stauch et al., (1989) Neurosci. Lett. 100: 295-300; and
11. Curt et al., (1985) J. Clin. Invest. 76: 1323-1329.

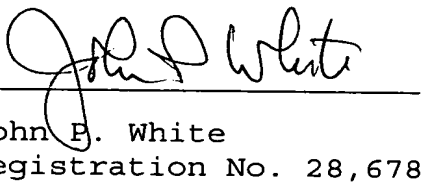
This Supplemental Information Disclosure Statement is being submitted under 37 C.F.R. §1.97(c) and a check including the amount of ONE HUNDRED AND EIGHTY DOLLARS ($180.00) is enclosed herewith.

Applicants request the Examiner consider the items listed herein and make them of record in the subject application.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the total enclosed fee of $690.00, including a $180.00 Information Disclosure Statement fee and a $510.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment and Supplemental Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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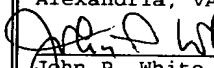

2/2/07

John P. White Date
Reg. No. 28,678

Jpn J Clin Oncol. 1995 Aug;25(4):124-30.

# Influence of systemic chemotherapy on anti-P-glycoprotein antibody-dependent cell-mediated cytotoxicity in patients with small cell lung cancer.

Nabioullin R, Yanagawa H, Haku T, Hiramatsu K, Yano S, Hanibuchi M, Pai K, Tsuruo T, Sone S.

Third Department of Internal Medicine, University of Tokushima School of Medicine.

Anti-P-glycoprotein antibody (MRK-16)-dependent cell-mediated cytotoxicity (ADCC) by blood mononuclear cells (MNC) was examined in patients with small cell lung cancer (SCLC) before and after systemic chemotherapy. The effect of in vitro treatment of MNC with interleukin (IL)-2 and macrophage-colony-stimulating factor (M-CSF) was also examined. The ADCC reaction was assessed by a 6 h 51Cr-release assay using a multidrug-resistant (MDR) SCLC cell line (H69/VP cells). The MRK-16 monoclonal antibody was able to augment spontaneous cytotoxicity by MNC, even in SCLC patients. Pretreatment of MNC with IL-2 significantly augmented their ADCC ability in SCLC patients, while M-CSF had no effect on ADCC activity. After the first cycle of systemic chemotherapy, the ADCC activity tended to decline, but ADCC of MNC pretreated with IL-2 was not affected. The results suggest that anti-P-glycoprotein antibody, in combination with a cytokine such as IL-2, may be therapeutically useful against human SCLC resistant to chemotherapeutic drugs.

PMID: 7666588 [PubMed - indexed for MEDLINE]

J Urol. 1995 Jul;154(1):288-92.

# Reactivities of mouse monoclonal antibody K2.7 to renal cancers in complement dependent cytotoxicity and antibody dependent cell-mediated cytotoxicity.

Kinouchi T, Bander NH, Kotake T.

Department of Urology, Center for Adult Diseases, Osaka, Japan.

Immunohistochemical analysis by indirect immunoperoxidase staining demonstrated that monoclonal antibody (mAb) K2.7, derived from a mouse immunized with a renal cell carcinoma (RCC) cell line OS-RC-2, reacted with 89 of 95 renal cancer tissues (94%). Only 1 gastric and uterine cancer tissue showed positive staining among 87 cancer specimens from 9 different organs. Among normal human tissues, the renal tubule, testis, epithelium of the uterine endometrial gland and Fallopian tube, grey matter of cerebrum and cerebellum, and foreskin showed positive staining. Serological analysis by protein A mixed hemadsorption (PA) assay demonstrated that mAb K2.7 reacted with 25 of 31 RCC cell lines (81%), but with only 2 of 50 other cell lines from different organs. The specific antitumor activities of mAb K2.7 against RCC cell lines were investigated in vitro by complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC) assays. In the CDC assay, all of the 9 RCC cell lines reactive serologically with mAb K2.7 were killed by mAb K2.7 with normal human serum, and the killing activity of mAb K2.7 correlated well with the reactivity of mAb K2.7 in the PA assay. mAb K2.7 showed the same killing activity against each of 3 RCC cell lines with sera from 9 patients with low and high stage renal cancers, as well as with normal human serum. In the ADCC assay, mAb K2.7 with peripheral blood leukocytes (PBLs) from 4 healthy donors showed cytotoxic activity against RCC cell lines. Peripheral blood leukocytes from the same 9 renal cancer patients also showed significant killing activity against the 3 RCC cell lines. These findings suggest the potential utility of mAb K2.7 for specific immunotherapy of renal cancer.

PMID: 7776448 [PubMed - indexed for MEDLINE]